Remarks

As a result of telephonic interview between the Examiner and applicants' representative, attached hereto are data previously submitted in former Office Actions. In accordance with the Examiner's suggestion, applicants have placed the data in a 132 Declaration.

Applicants have amended the title from Pirazino(aza)indoline Derivatives to Pirazino Indoline Derivatives.

Claim 1 has been amended to capture the classes of compounds for which the applicants have demonstrated evidence of unexpected results. Support for this amendment is found throughout the application. See the working examples as well as page 5, lines 9, 17-18 and 21, and page 7, lines 9-11 and 13-15. Claim 34 has been amended to be independent by adding the relevant recitations of previous claim 1 and in accordance with the Office Action dated August 29, 2003, is now allowable.

IDS

The Examiner has not initialed all the references of the Form 1449 of the IDS filed on November 9, 2001. Specifically, the A3 reference to Mokrosz is not initialed. Applicants attach hereto a copy of the IDS and Form 1449 filed on November 9, 2001, as well as the OIPE stamped post card confirming the PTO's receipt thereof. In accordance with MPEP § 609 III C(2), applicants respectfully request a return of the Form 1449 filed on November 9, 2001 wherein reference A3 has been initialed.

Claim Objections

Amended claim 1 recites haloalkyl, which at page 5, line 18 of the specification, is explicitly exemplified with trifluoromethyl. Therefore, claim 11 is in proper dependent format.

Rejections Under 35 USC103(a)

Obviousness over Mokrosz

Mokrosz discloses compounds without substituents on the phenyl ring. Applicants

resubmit comparative data in a 132 Declaration showing superior properties for compounds in which the phenyl ring was substituted by F, Cl, Br, Me, Et, CF_3, OCF_3 and/or MeS and have amended the claims to capture the classes of compounds for which the applicants have demonstrated evidence of unexpected results. The efficacy of the compounds of the present claims is supported by the data submitted to the PTO on December 6, 2002 and April 24, 2003, now in a 132 Declaration.

Applicants wish to address one point of the Examiner's argument which is of particular concern. At the bottom of page 4, the Examiner states "Additionally, applicants should note the prior art N-ethyl piperazine as shown by Mokrosz *et al.* is active at the 5HT receptor and hence one would be motivated to make and evaluate the compound with a methyl group in the ring." This allegation has no foundation because the methyl substituent is unexpectedly superior and applicants have already shown this by the comparative data previously submitted.

Obviousness over Jonas (US-3853878) in view of Mokrosz

The Examiner combines an intermediate from Jonas with the disclosure of Mokrosz and concludes that the Jonas and Mokrosz combination would lead the skilled person to the present invention.

Applicants contend that this rejection is improper because the Examiner has not shown that one of ordinary skill in the art would have had the requisite motivation to combine these references. There is no suggestion at all in Jonas that the methoxy-substituted intermediate compounds were pharmacologically active. Jonas teaches that the pharmacological activity requires the presence of the N-carboxamidine group on the pyrazino ring which is absent from Mokrosz's compounds, and absent from the compounds of the present invention. Because Jonas makes no suggestion for the pharmacological use of the intermediates which have no carboxamidine on the pyrazino ring, the skilled person would not consider that these intermediates were active. As such, there is nothing which would teach one of ordinary skill in the art to modify the compounds of Mokrosz by putting a methoxy substituent on the phenyl ring as taught by Jonas. Equally, there is nothing taught by Mokrosz which would suggest to one of ordinary skill in the art that he should modify Jonas's active compounds by removing the carboxamidine group.

The Examiner's comment that "The combined art teaches equivalency of the

intermediate compounds with bioactive compounds and hence its pharmaceutical composition" is without foundation.

Moreover, Jonas teaches the use of his compounds for their blood-pressure lowering properties. Mokrosz teaches that his compounds are active at 5HT receptors. There is nothing in either of these two documents which would suggest activity in the target disorder of the other, which is a further reason why there is no motivation to combine the two disclosures.

In summary, there is no motivation for one of ordinary skill in the art to modify the compounds of one document in view of those of the other document in a manner which would result in the compounds of the present invention.

Obviousness over Bos in view of Mokrosz

The Examiner refers to "Bos CA 2097," which applicants presume to mean CA-2097465. Bos teaches tetrahydropyrazinoindoles, whereas Mokrosz teaches tetra- and hexahydropyrazinoindoles. Applicants traverse the Examiner's allegation that: "there is a clear-cut teaching of equivalency of both tetrahydropyrazinoindole and hexahydropyrazinoindole in their activity toward 5HT" for the reasons that follow.

A structural difference of the presently claimed compounds over those of Bos is that the C-10 position in the presently claimed compounds is saturated whereas the compounds of Bos contain a double bond in this position.

The Examiner says that the teaching of Mokrosz would motivate the skilled person to modify the compounds of Bos in a manner which would result in the presently claimed compounds, i.e. by saturating this double bond. A careful review of the prior art shows that this is not the case for the following reasons.

When one compares compounds (5) and (6) of Mokrosz, which both have an unsubstituted (-NH) group in the piperazine ring, it can be seen that the unsaturated compound (5) has a K_i ($5HT_2$) of 1800nM whereas the saturated compound (6) has a higher K_i ($5HT_2$) of 3570nM. In addition, when compounds (7) and (8) are compared, which both have an -N(Et) group in the piperazine ring, it can be seen that the unsaturated compound (8) has a K_i ($5HT_2$) of 3610nM whereas the saturated compound (7) has a higher K_i ($5HT_2$) of 3780nM. In both instances, therefore, the saturated compound has a higher K_i and is therefore less strongly binding than the unsaturated compound.

Accordingly, one of ordinary skill in the art, starting from the disclosure of Bos as the closest prior art, would not be motivated to modify the compounds of Bos on the basis of Mokrosz because Mokrosz shows that removing the unsaturation leads to a reduction in the binding affinity. Thus, a combination of Bos and Mokrosz would not lead one of ordinary skill in the art to the compounds of claim 1. Therefore the claimed subject-matter is, *prima facie*, non-obvious.

Respectfully submitted,

Date January 29, 2004

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

FOLEY & LARDNER

040283-0192

November 9, 2001

APPLICANT: David Reginald ADAMS et al.
SERIAL NO.: 09/890,186
FILING DATE: 10/09/2001 ← 7/30/01
FOR: PIRAZINO(AZA)INDOLE DERIVATIVES

(29)

XX Information Disclosure Statement\PTO-1449\3 references

____ International Search Report

Due: November 12, 2001

Return to: BDS\nd\hh

QR: ; INSP:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NO. 040283-0192

Applicant: David Reginald ADAMS et al.

Title: PIRAZINO(AZA)INDOLE DERIVATIVES

Appl. No.: 09/890,186

Filing Date: 10/09/2001

Examiner: Unassigned

Art Unit: Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith on Form PTO-1449 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56. A copy of each listed document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

RELEVANCE OF EACH DOCUMENT

All of the documents are in English.

Applicants respectfully request that any listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO-1449 be returned in accordance with MPEP §609.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

November 9, 2001
Date

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Form PTO-1449 (MODIFIED)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. 040283-0192	SERIAL NO. 09/890,186
		APPLICANT David Reginald ADAMS et al.	
		FILING DATE 10/09/2001	GROUP ART UNIT Unassigned

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
	A1	2,132,887	04/23/95	CANADA				
	A2	2,097,465	12/06/93	CANADA				

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

	A3	MOKROSZ et al., "Structure Activity Relationship Studies of CNS Agents on the Bioactive Conformation of 1-Arylpiperazines Once More," Medicinal Chemistry Research, Birkhauser Boston, Vol. 3, pp. 240-248, (1993).

EXAMINER	DATE CONSIDERED

* **EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include any copy of this form with next communication to applicant.**